

# Genotypes and Haplotypes

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# Goals

- Gaps in the science
- Methodologic issues and barriers
- Future directions

# Workshop Outcomes

- Haplotype structure – esp minority populations
- Education guidelines & resources
- Analytic methods development
- Biosamples
- Informed consent
- Encourage re-analysis, secondary analysis
- Roadmap approach across institutes for resequencing efforts

# Workshop Outcomes (1)

## Haplotypes in minorities

- resequencing efforts? Centralized?
- Moving target...delta populations dynamics
- participations rate
- Interactions of genomicists and epidemiologists
  - educating the intersection (AACR-ASHG-education sessions, IGES-MEG,ongoing dialogue, GAW.
- Strategies for doing haplotypes: pooling vs single genes
- Are biosamples needed in ALL case-control studies? Does it make sense to start new case-control studies? Required in PA, opportunity cost.

# Workshop Outcomes (2)

- Informed consent/HIPAA: De-novo case-control studies: access to investigators.
- Too soon for dogma: Educational guidelines/resources to encourage/define multiple approaches in haplotype-based approaches
- Roadmap approach (cross-institutes) for re-sequencing SNP'. Better links to available informatics resources
- Promoting methodologic development, incorporating environment. Technology and analysis
- Encourage secondary analysis of data for methods comparison
- Larger role of NCI to encourage collaborative re-analysis, secondary analysis

# Workshop Outcomes (3)

- Encourage journals to leave results online for extended period/publish negative data
- Genetic variations within regulatory regions...non-coding. Guidelines on how to prioritize/educational session (foster interrogation of non-coding regions)
- Look at studies of underrepresented populations in US to examine genetic variation
- Methods development for methylation/epigenetics.

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# Population Stratification

## *Haplotypes to the Rescue?*

Dopamine Receptor D2 – polymorphisms & smoking

DRD2	Caucasians	A1/B1	$r = 0.76$ $D' = 0.464$
DRD2	Mexican-Americans	A1/B1	
DRD2	Japanese men	A2/B2	

*Spitz et al, JNCI 1998;90:358-63*

*Wu et al, CEBP 2000; 9:1021-26*

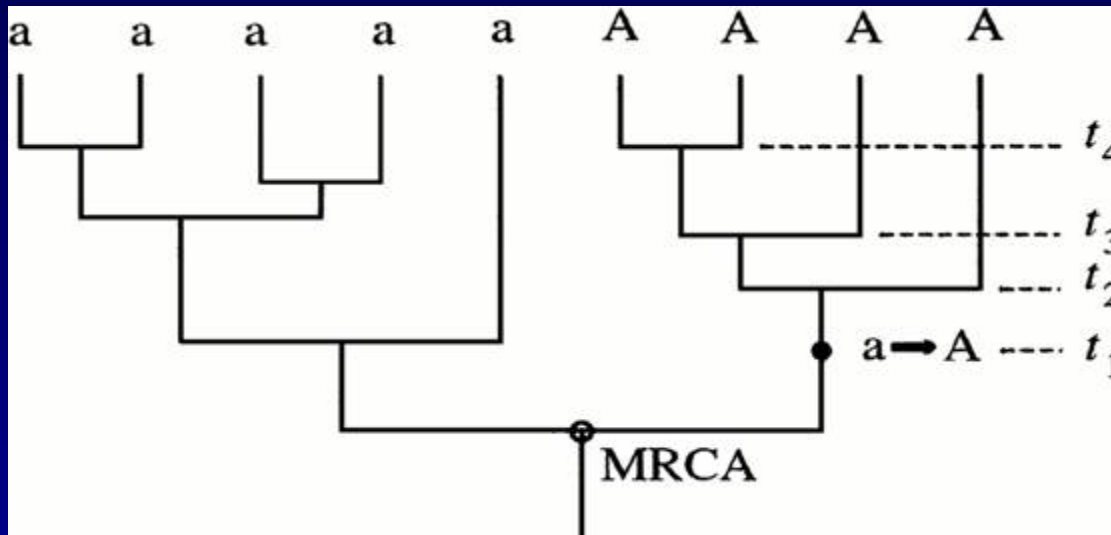
*Hamjima et al. J Epidemiol. 2002 Jul;12(4):297-30*



# Different effects in Distinct Populations offers Insight

- Smoking probability and intensity associated with:
  - B1 in Caucasians ( $p < 0.02$ )
  - A1 allele in Mexican Americans ( $p < 0.06$  linear trend)
  - A2/A2 genotype in Japanese men OR= 2.32 (1.02-5.29)
  - A2 allele in Chinese Han ( $p < 0.047$ )

# Genealogy Ages for Estimation



From Slatkin and Rann  
2000

Estimate allele age using intra-allelic variability: variations in sequence at closely linked polymorphic markers, among alleles containing polymorphism of interest

# Date of I1307K Most Common Ancestor 195 BC – 947 BC



Niell et al, Am J Human Genet 2003; 73:1250-60